

AMENDMENTS TO THE CLAIMS

1. **(Currently Amended)** A method of screening a physiologically active substance, comprising the steps of:
 - a) ~~contacting a test sample with a transformed yeast with a test sample~~capable of expressing a protein involved in proliferation or differentiation of cells or regulating cell cycles of a mammalian cell, wherein the transformed yeast is respiration ability deficient and show ~~is capable of expressing a heterogeneous protein, and shows a change in the growth rate of said transformed yeast; a growing state in an expression state of the protein as compared to that in a non-expression state of the protein;~~
 - b) ~~culturing the said transformed yeast under conditions that~~ result in expression of said the protein is capable of being expressed; and
 - c) ~~measuring the growing state growth rate of the said cultured yeast,~~wherein the physiologically active substance is judged to be present in the test sample in a case where the growth of the yeast is lowered or improved in the presence of the test sample as compared to that in the absence of the test sample as a control.
2. **(Currently Amended)** The method of screening according to claim 1, wherein expression of the heterogeneous said protein is capable of causes lowering the growth rate of the said transformed yeast as compared to a culture of said transformed yeast that is not expressing said protein.~~that of the non-expression state.~~
3. **(Currently Amended)** The method of screening according to claim 1 or 2, wherein the ~~heterogeneous said~~ protein is ~~a protein involved in regulating cell cycle of a mammal cell.~~
4. **(Currently Amended)** The method of screening according to claim 3, wherein ~~the said protein involved in regulating cell cycle of a mammal cell is a protein involved in intracellular signaling of GO/G1 phase of a mammal cell.~~

5. **(Currently amended)** The method of screening according to claim 1, wherein the ~~growing state growth rate of the said transformed yeast is determined in the step (3) by~~ monitoring a change in at least one member selected from the group consisting of the turbidity of an yeast culture medium, a morphological change of the yeast, a change in wet-weight of the yeast, a change in dry-weight of the yeast, a change in endogenous enzyme activity of the yeast or a change in amount of an endogenous protein of the yeast.
6. **(Canceled)**
7. **(Withdrawn)** A transformed yeast being capable of expressing a heterogeneous protein, and showing a change in a growing state in an expression state of the protein as compared to that in a non-expression state of the protein.
8. **(Withdrawn)** The transformed yeast according to claim 7, wherein the change in the growing state is lowering of the growth.
9. **(Withdrawn)** The transformed yeast according to claim 7 or 8, wherein the heterogeneous protein comprises at least an active site of the protein in an active state.
10. **(Withdrawn)** The transformed yeast according to claim 7, wherein the heterogeneous protein is a protein involved in regulating cell cycle of a mammal cell.
11. **(Withdrawn)** The transformed yeast according to claim 10, wherein the protein involved in regulating cell cycle of a mammal cell is a protein involved in intracellular signaling of G0/G1 phase of a mammal cell.
12. **(Withdrawn)** The transformed yeast according to claim 11, wherein the protein involved in intracellular signaling of G0/G1 phase of a mammal cell is a protein belonging to Tob family and/or a protein belonging to Caf family.

13. **(Withdrawn)** The transformed yeast according to claim 12, wherein the protein belonging to Tob family is:
- (a) a protein comprising in an N-terminal region of the amino acid sequence thereof the amino acid sequence of SEQ ID NO: 1;
 - (b) a protein comprising in an N-terminal region of the amino acid sequence thereof an amino acid sequence having deletion, addition, insertion or substitution of at least one amino acid residue in the amino acid sequence of SEQ ID NO: 1, wherein the protein induces growth inhibition of the transformed yeast in the expression state;
 - (c) a protein comprising in an N-terminal region of the amino acid sequence thereof an amino acid sequence having a sequence identity of 20% or more to the amino acid sequence of SEQ ID NO: 1, wherein the protein induces growth inhibition of the transformed yeast in the expression state; or
 - (d) a protein comprising in an N-terminal region of the amino acid sequence thereof an amino acid sequence having a sequence identity of 20% or more to the amino acid sequence of SEQ ID NO: 2 in a region from an N-terminal to 100 amino acid residues, wherein the protein induces growth inhibition of the transformed yeast in the expression state.
14. **(Withdrawn)** The transformed yeast according to claim 12, wherein the protein belonging to Caf family is:
- (a) a protein comprising the amino acid sequence of SEQ ID NO: 4;
 - (b) a protein comprising an amino acid sequence having deletion, addition, insertion or substitution of at least one amino acid residue in the amino acid sequence of SEQ ID NO: 4, wherein the protein induces growth inhibition of the transformed yeast in the expression state; or
 - (c) a protein comprising an amino acid sequence having a sequence identity of 20% or more to the amino acid sequence of SEQ ID NO: 4,

wherein the protein induces growth inhibition of the transformed yeast in the expression state.

15. **(Withdrawn)** The transformed yeast according to claim 7, wherein the transformed yeast comprising a gene encoding a heterogeneous protein operably in expression ligated to a promoter.
16. **(Withdrawn)** The transformed yeast according to claim 7, wherein the transformed yeast is deficient of aspiration ability, which is used for the method of screening comprising the steps of:
 - (1) contacting a transformed yeast with a test sample, wherein the transformed yeast is capable of expressing a heterogeneous protein, and shows a change in a growing state in an expression state of the protein as compared to that in a non-expression state of the protein;
 - (2) culturing the yeast under conditions that the protein is capable of being expressed; and
 - (3) measuring the growing state of the yeast,wherein the physiologically active substance is judged to be present in the test sample in a case where the growth of the yeast is lowered or improved in the presence of the test sample as compared to that in the absence of the test sample as a control.
17. **(Withdrawn)** A physiologically active substance obtainable by the method of screening as defined in claim 1.
18. **(Withdrawn)** A kit for screening a physiologically active substance, comprising the yeast as defined in claim 7.
19. **(New)** A method of screening for a physiologically active substance, comprising:

- (a) culturing a test culture comprising a test physiologically active substance and a yeast transformed with a recombinant expression vector, wherein said transformed yeast is respiration deficient and has a sensitized growth rate due to the expression of a heterogeneous protein encoded by said vector, and wherein said protein controls the proliferation of mammalian cells or regulates the cell cycle of mammalian cells ;
 - (b) measuring a growth state of said transformed yeast in said test culture;
 - (c) culturing a control culture of said transformed yeast;
 - (d) measuring a growth state of said control culture; and
 - (e) comparing the growth states of said test and control cultures;
- wherein said test physiologically active substance is judged to have physiological activity where the growth state of said transformed yeast in said test culture is lowered or improved as compared to the growth rate of said yeast in said control culture.
- 20. **(New)** The method of screening according to claim 1 or 19, wherein said protein is a Tob family protein and/or a Caf family protein.
 - 21. **(New)** The method of screening according to claim 19, wherein the amino acid sequence of said protein comprises an amino acid sequence having a sequence identity of 90% or more to the amino acid sequence of SEQ ID NO: 1.
 - 22. **(New)** The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises an amino acid sequence having a sequence identity of 90% or more to the amino acid sequence of SEQ ID NO: 1
 - 23. **(New)** The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises the amino acid of SEQ ID NO: 1.

24. (New) The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises an amino acid sequence having a sequence identity of 95% or more to the amino acid sequence of SEQ ID NO: 2.
25. (New) The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises an amino acid sequence having a sequence identity of 90% or more to the amino acid sequence of SEQ ID NO: 2.
26. (New) The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises an amino acid sequence having the amino acid sequence of SEQ ID NO: 2.
27. (New) The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises an amino acid sequence having a sequence identity of 95% or more to the amino acid sequence of SEQ ID NO: 4.
28. (New) The method of screening according to claim 20, wherein the amino acid sequence of said protein comprises an amino acid sequence having the amino acid sequence of SEQ ID NO: 4.